

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents
United States Patent and Trademark
Office
Box PCT
Washington, D.C. 20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 08 February 2000 (08.02.00)	Applicant's or agent's file reference PG3506/PCT
International application No. PCT/GB99/02199	Priority date (day/month/year) 11 July 1998 (11.07.98)
International filing date (day/month/year) 09 July 1999 (09.07.99)	
Applicant BRADDOCK, Martin et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:
20 December 1999 (20.12.99)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was
☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

M.H

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference PG3506/PCT	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/GB 99/ 02199	International filing date (day/month/year) 09/07/1999	(Earliest) Priority Date (day/month/year) 11/07/1998
Applicant GLAXO GROUP LIMITED et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

☐ the text is approved as submitted by the applicant.

☒ the text has been established by this Authority to read as follows:

PHARMACEUTICAL USES OF NAB1 AND NAB2

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☒ None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB 99/02199

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 16 and 21 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

national Application No

PCT/GB 99/02199

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N15/12 A61K48/00 A61K38/17

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	SHAH ET AL: "NEUTRALIZING ANTBODY TO TGF-BETA1,2 REDUCES CUTANEOUS SCARRING IN ADULT RODENTS" JOURNAL OF CELL SCIENCE, vol. 107, 1994, pages 1137-1157, XP002123674 cited in the application page 1150, paragraph 3 -page 1155, paragraph 1 --- -/--	1-22

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

1 December 1999

Date of mailing of the international search report

15/12/1999

Name and mailing address of the ISA

 European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax: (+31-70) 340-3016

Authorized officer

Sitch, W

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 99/02199

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	LIU C ET AL: "Transcription factor EGR - 1 suppresses the growth and transformation of human HT-1080 fibrosarcoma cells by induction of transforming growth factor beta 1." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1996 OCT 15) 93 (21) 11831-6. , XP002123675 page 11831 abstract page 11834, paragraph 3 -page 11835, paragraph 1 ---	1-22
A	RUSSO M W ET AL: "IDENTIFICATION OF NAB1 A REPRESSOR OF NGFI-A- AND KROX20-MEDIATED TRANSCRIPTION" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA,US,NATIONAL ACADEMY OF SCIENCE. WASHINGTON, vol. 92, page 6873-6877 XP002034500 ISSN: 0027-8424 cited in the application page 6873 abstract ---	
A	SVAREN J. ET AL: "NAB2 A COREPRESSOR OF NGFI-A (EGR-1) AND KROX20 IS INDUCED BY PROLIFERATIVE AND DIFFERENTIATIVE STIMULI" MOLECULAR AND CELLULAR BIOLOGY,US,WASHINGTON, DC, vol. 16, no. 7, page 3545-3553 XP002034499 ISSN: 0270-7306 cited in the application page 3545 abstract ---	
A	KHACHIGIAN ET AL: "EGR-1-INDUCED ENDOTHELIAL GENE EXPRESSION: A COMMON THEME IN VASCULAR INJURY" SCIENCE, vol. 271, 1996, pages 1427-1431, XP002123676 page 1430; figure 4 ---	
A	US 5 036 006 A (SANFORD JOHN C ET AL) 30 July 1991 (1991-07-30) column 6, line 49 -column 8, line 68 ---	8-10
A	US 5 697 901 A (ERIKSSON ELOF) 16 December 1997 (1997-12-16) column 2, line 66 -column 5, line 20 --- -/--	8,11

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/GB 99/02199

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, Y	QU ET AL: "THE TRANSCRIPTIONAL COREPRESSOR NAB2 INHIBITS NGF-INDUCED DIFFERENTIATION OF PC12 CELLS" THE JOURNAL OF CELL BIOLOGY, vol. 142, no. 4, 24 August 1998 (1998-08-24), pages 1075-1082, XP002123677 cited in the application page 1075 abstract page 1079, paragraph 3 -page 1080, paragraph 1 page 1080; figure 6 -----	1-22

INTERNATIONAL SEARCH REPORT

ation on patent family members

International Application No

PCT/GB 99/02199

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5036006 A	30-07-1991	US 4945050 A	31-07-1990
		US 5478744 A	26-12-1995
		US 5100792 A	31-03-1992
		US 5371015 A	06-12-1994
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US 5697901 A	16-12-1997	US 5423778 A	13-06-1995
		US 5152757 A	06-10-1992
		US 5661132 A	26-08-1997
		AU 4535693 A	04-01-1994
		EP 0644929 A	29-03-1995
		EP 0955359 A	10-11-1999
		JP 8509356 T	08-10-1996
		WO 9325660 A	23-12-1995
		AT 145563 T	15-12-1996
		AU 650440 B	23-06-1994
		AU 7176391 A	18-07-1991
		CA 2071827 A,C	15-06-1991
		DE 69029275 D	09-01-1997
		DE 69029275 T	12-06-1997
		DK 505478 T	12-05-1997
		EP 0505478 A	30-09-1992
		ES 2097803 T	16-04-1997
		GR 3022710 T	31-05-1997
		JP 2535694 B	18-09-1996
		WO 9108793 A	27-06-1992
<hr/>			

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PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : C12N 15/12, A61K 48/00, 38/17		A1	(11) International Publication Number: WO 00/03014
			(43) International Publication Date: 20 January 2000 (20.01.00)
(21) International Application Number: PCT/GB99/02199		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).	
(22) International Filing Date: 9 July 1999 (09.07.99)		Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
(30) Priority Data: 9814989.1 11 July 1998 (11.07.98) GB 9819826.0 12 September 1998 (12.09.98) GB			
(71) Applicant (for all designated States except US): GLAXO GROUP LIMITED [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).			
(72) Inventors; and (75) Inventors/Applicants (for US only): <u>BRADDOCK</u> , Martin [GB/GB]; Glaxo Wellcome plc, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). <u>CAMPBELL</u> , Callum, Jeffrey [GB/GB]; Glaxo Wellcome plc, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB).			
(74) Agent: LEAROYD, Stephanie, Anne; Glaxo Wellcome plc, Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).			
(54) Title: PHARMACEUTICAL USES OF NAB1 AND NAB2			
(57) Abstract The invention relates to the use, particularly in gene therapy, of an NAB1 or NAB2 polypeptide or a biologically active fragment thereof, and to nucleic acid molecules encoding such polypeptides, in the manufacture of a medicament for the treatment of cell proliferation disorders associated with wound healing in a mammal, including human.			

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
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DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/GB 99/02199

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N15/12 A61K48/00 A61K38/17

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>SHAH ET AL: "NEUTRALIZING ANTIBODY TO TGF-BETA1,2 REDUCES CUTANEOUS SCARRING IN ADULT RODENTS"</p> <p>JOURNAL OF CELL SCIENCE, vol. 107, 1994, pages 1137-1157, XP002123674</p> <p>cited in the application</p> <p>page 1150, paragraph 3 -page 1155, paragraph 1</p> <p style="text-align: center;">---</p> <p style="text-align: center;">-/--</p>	1-22

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

1 December 1999

Date of mailing of the international search report

15/12/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Sitch, W

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 99/02199

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>LIU C ET AL: "Transcription factor EGR - 1 suppresses the growth and transformation of human HT-1080 fibrosarcoma cells by induction of transforming growth factor beta 1."</p> <p>PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1996 OCT 15) 93 (21) 11831-6. , XP002123675</p> <p>page 11831</p> <p>abstract</p> <p>page 11834, paragraph 3 -page 11835, paragraph 1</p> <p style="text-align: center;">---</p>	1-22
A	<p>RUSSO M W ET AL: "IDENTIFICATION OF NAB1 A REPRESSOR OF NGFI-A- AND KROX20-MEDIATED TRANSCRIPTION"</p> <p>PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA,US,NATIONAL ACADEMY OF SCIENCE. WASHINGTON, vol. 92, page 6873-6877 XP002034500</p> <p>ISSN: 0027-8424</p> <p>cited in the application</p> <p>page 6873</p> <p>abstract</p> <p style="text-align: center;">---</p>	
A	<p>SVAREN J ET AL: "NAB2 A COREPRESSOR OF NGFI-A (EGR-1) AND KROX20 IS INDUCED BY PROLIFERATIVE AND DIFFERENTIATIVE STIMULI"</p> <p>MOLECULAR AND CELLULAR BIOLOGY,US,WASHINGTON, DC, vol. 16, no. 7, page 3545-3553</p> <p>XP002034499</p> <p>ISSN: 0270-7306</p> <p>cited in the application</p> <p>page 3545</p> <p>abstract</p> <p style="text-align: center;">---</p>	
A	<p>KHACHIGIAN ET AL: "EGR-1-INDUCED ENDOTHELIAL GENE EXPRESSION: A COMMON THEME IN VASCULAR INJURY"</p> <p>SCIENCE, vol. 271, 1996, pages 1427-1431, XP002123676</p> <p>page 1430; figure 4</p> <p style="text-align: center;">---</p>	
A	<p>US 5 036 006 A (SANFORD JOHN C ET AL)</p> <p>30 July 1991 (1991-07-30)</p> <p>column 6, line 49 -column 8, line 68</p> <p style="text-align: center;">---</p>	8-10
A	<p>US 5 697 901 A (ERIKSSON ELOF)</p> <p>16 December 1997 (1997-12-16)</p> <p>column 2, line 66 -column 5, line 20</p> <p style="text-align: center;">---</p> <p style="text-align: center;">-/--</p>	8,11

INTERNATIONAL SEARCH REPORT

Inter. Appl. No.

PCT/GB 99/02199

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, Y	<p>QU ET AL: "THE TRANSCRIPTIONAL COREPRESSOR NAB2 INHIBITS NGF-INDUCED DIFFERENTIATION OF PC12 CELLS" THE JOURNAL OF CELL BIOLOGY, vol. 142, no. 4, 24 August 1998 (1998-08-24), pages 1075-1082, XP002123677 cited in the application page 1075 abstract page 1079, paragraph 3 -page 1080, paragraph 1 page 1080; figure 6 -----</p>	1-22

INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB 99/ 02199

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 16 and 21 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

information on patent family members

Inter. Appl. No.

PCT/GB 99/02199

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5036006 A	30-07-1991	US 4945050 A	31-07-1990
		US 5478744 A	26-12-1995
		US 5100792 A	31-03-1992
		US 5371015 A	06-12-1994
US 5697901 A	16-12-1997	US 5423778 A	13-06-1995
		US 5152757 A	06-10-1992
		US 5661132 A	26-08-1997
		AU 4535693 A	04-01-1994
		EP 0644929 A	29-03-1995
		EP 0955359 A	10-11-1999
		JP 8509356 T	08-10-1996
		WO 9325660 A	23-12-1995
		AT 145563 T	15-12-1996
		AU 650440 B	23-06-1994
		AU 7176391 A	18-07-1991
		CA 2071827 A,C	15-06-1991
		DE 69029275 D	09-01-1997
		DE 69029275 T	12-06-1997
		DK 505478 T	12-05-1997
		EP 0505478 A	30-09-1992
		ES 2097803 T	16-04-1997
		GR 3022710 T	31-05-1997
		JP 2535694 B	18-09-1996
		WO 9108793 A	27-06-1992

PCT

REC'D 26 OCT 2000

INTERNATIONAL PRELIMINARY EXAMINATION REPORT PCT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PG3506/PCT	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/GB99/02199	International filing date (day/month/year) 09/07/1999	Priority date (day/month/year) 11/07/1998
International Patent Classification (IPC) or national classification and IPC C12N15/12		
Applicant GLAXO GROUP LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 6 sheets, including this cover sheet.

- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☒ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 20/12/1999	Date of completion of this report 23.10.2000
Name and mailing address of the international preliminary examining authority:  European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized officer Sitch, W Telephone No. +31 70 340 3040 

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB99/02199

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-37 as originally filed

Claims, No.:

1-22 as originally filed

Drawings, sheets:

1/10-10/10 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
☒ claims Nos. 1-22 with respect to industrial applicability.

because:

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- ☒ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

- ☐ no international search report has been established for the said claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-22
	No:	Claims	None
Inventive step (IS)	Yes:	Claims	None
	No:	Claims	1-22
Industrial applicability (IA)	Yes:	Claims	1-22 (see separate sheet)
	No:	Claims	

2. Citations and explanations

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

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Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 1-22 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

- D1: Journal of Cell Science, vol. 107, 1994, 1137-1157
- D2: Proc. Natl. Acad. Sci., USA, vol. 93, 1996, 11831 - 11836
- D3: US5036006
- D4: US5697901

1. The claims of the present application do not meet the requirement of Art. 33(3), PCT with regard to inventive step.

1.1 D1 represents the closest prior art and discloses the pivotal role of TGF-Beta1 in wound healing. The document discloses that addition of a neutralizing antibody to TGF-Beta1,2 reduces scar formation after cutaneous injury. Early application of antibody achieved good results, whereby the effects are stated as probably being due to reduction in level of TGF-Beta at the wound site. See page 1150, paragraph 3 - page 1155, paragraph 1.

The subject matter of claims 1, 14-17, 21, 22 differs from D1 in that an NAB1 or NAB2 polypeptide or encoding nucleic acid is a technical feature of each of these claims. The problem to be solved is to provide alternative means of treating cell proliferative disorders associated with wound healing.

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D2 discloses the effects of Egr-1 on induction of TGFβ1 in fibrosarcoma cells, and that addition of TGF-β1 is strongly growth-suppressive for the cells. Addition of anti-TGF-β1 antibody is shown to reverse the Egr-1 mediated growth inhibitory effects on the fibrosarcoma cells. See page 11831, abstract. It is concluded that Egr-1 suppresses growth of the cells via induction of TGF-β1. Additionally, mention is made on page 11834, paragraph 3 - page 11835, paragraph 1, that the presence of the Egr-1 corepressors NAB1 and NAB2 may be reducing the activation of TGF-β1 by Egr-1 in the cells being studied. To test this, transactivation of a TGF-β1 reporter construct by Egr-1 mutants unable to interact with NAB1 and NAB2 was studied. Higher levels of transactivation were achieved in such a study (see figure 5 on page 11835), from which the skilled person would conclude that NAB1 and NAB2 have a repressing effect on TGF-β1 activity via interaction with Egr-1.

Aware from D1 that suppression of the effects of TGF-β1 by antibody (ie repression of TGF-β1 by a method other than that of the present application) can have beneficial effects in improving wound healing via mechanisms including decreasing macrophage and monocyte numbers at the wound site (D1, above passages), and aware from D2 that NAB1 / NAB2 can repress TGF-β1 via Egr-1, the skilled person, seeking to solve the above-mentioned problem, would seek to achieve desirable down regulation of TGF β1 in wound healing by methods other than that of D1, including, in light of D2, by the use of an NAB1 or NAB2. The use of NAB1 or NAB2 for the treatment of cell proliferative disorders associated with wound healing would thus be arrived at by the skilled person without exercising inventive skill. Since it is additionally of common knowledge to the skilled person that the in vivo effects of a polypeptide may be expected to be achieved by the in vivo delivery of a nucleic acid encoding such, the subject matter of claim 1 would be arrived at by the skilled person without exercising inventive skill, and the claim lacks inventive step.

The subject matter of independent claims 14, 15, 16, 17, 21 and 22 is also not inventive for the reasons given for claim 1.

1.2 The additional features of dependent claims 2-13 and 18-20 amount to those of common practise in the art and the claims are not inventive. In particular, those features of claims 8-11 relating to physical methods of nucleic acid delivery are disclosed in D3 (particle bombardment, see column 6, line 49 - column 8, line 68) and

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D4 (microseeding, see column 2, line 66 - column 5, line 20).

2. For the assessment of the present claims 1-22 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VII

Certain defects in the international application

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the document D2 is not mentioned in the description, nor is this document identified therein.